Domperidone IND Packet

For Patients with Gastrointestinal Disorders

1. Introduction

Domperidone is not currently a legally marketed drug or approved for sale in the U.S. On June 7, 2004, FDA issued a warning that compounding domperidone is illegal, and issued an import alert advising FDA field personnel that they may detain shipments of finished drug products and bulk ingredients containing domperidone. This warning was the result of the Agency's concern about the potential public health risks associated with the use of domperidone by lactating women to enhance breast milk production (i.e., the risk of cardiac arrhythmias, cardiac arrest, and sudden death outweigh the potential benefit of domperidone use in this population). These risks are also of concern in other populations that may use domperidone (such as patients with gastrointestinal motility disorders). Although the original reports of cardiac arrhythmias, cardiac arrest, and sudden death were with the intravenous form of domperidone, there have also been similar reports with the oral form of domperidone. Also, concomitant use of moderate or strong CYP3A4 inhibitors can lead to increased concentrations of domperidone, and thus increase the risk of cardiac arrhythmias, cardiac arrest, and sudden death. However, FDA recognized that there are some patients with severe gastrointestinal motility disorders that are difficult to manage with available therapy, who may benefit from domperidone and in whom domperidone's benefits outweigh its risks.

FDA currently allows patients 12 years of age and older with various gastrointestinal (GI) conditions to be treated with domperidone through the Expanded Access to Investigational Drugs program. These conditions include gastroesophageal reflux disease with upper GI symptoms, gastroparesis, and chronic constipation. Patients must have failed standard therapies to be eligible to receive domperidone. This program facilitates availability of investigational drugs, (such as domperidone) to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. Authorization must be obtained from FDA prior to the importation, interstate shipment, and administration of domperidone.

2. What is an IND?

An Investigational New Drug Application (IND) is a request for FDA authorization to administer an investigational new drug to humans. An IND allows for the importation, interstate shipment and administration of any drug that is not approved for sale in the U.S. (i.e., an investigational new drug). Domperidone is not approved for use in the United States; therefore it may not be shipped into the U.S. without an IND. IND regulations are contained in Title 21, Code of Federal Regulations, Part 312[1]. To help facilitate the IND process, the FDA has developed this packet which includes instructions specific to the requirements for obtaining an IND for domperidone. More information about domperidone INDs can be found at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm368736.htm.

3. How do I open an IND?

A physician may open an IND for a single patient or for multiple patients. To open an IND, the physician must submit an application that generally includes the following:

- Cover letter (see Attachment B)
- Form 1571* (see Attachment C)

[1] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

- Form 1572* (see Attachment D)
- Clinical protocol (see Attachment F)
- Copy of the Informed Consent document you will be using which will be reviewed by your IRB (see Attachment J)

*To retrieve FDA forms see http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm
General instructions for completing Form FDA 1571 and 1572, see:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571

The application should be submitted to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
Central Document Room
5901B Ammendale Road
Beltsville, MD 20705-1266

4. What happens after I submit the IND?

Upon receipt of the IND by FDA, an IND number will be assigned, and the application will be forwarded to the Division of Gastroenterology and Inborn Errors Products. The reviewing division will send a letter to you (the Sponsor-Investigator) providing notification of the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA person to whom questions about the application should be directed. Normally, you cannot initiate any studies (i.e., administer the investigational drug) until 30 days after the date FDA receives the IND, unless you receive earlier notification from FDA that studies may begin. The 30 days provides the time needed by FDA to ensure that the proposed use of the investigational drug is reasonably safe and that all requirements have been met.

5. What are my responsibilities as a Sponsor-Investigator of an IND?

Your ongoing responsibilities as the Sponsor-Investigator of an IND include:
- Obtaining informed consent of patients to be treated under the IND
- Monitoring patients treated under the IND
- Maintaining control of and keeping records on the drug dispensed under the IND
- Notifying FDA of any changes made to the IND (e.g., changes to the protocol, a change in drug supplier)
- Reporting to FDA serious, fatal, and/or life-threatening adverse events that are associated with use of the drug (see Attachment H)
- Submitting an annual report to the IND (see Attachment I) within 60 days of the anniversary date you are permitted to initiate studies (i.e., begin administering the investigational drug) which is usually 30 days after FDA receives the application.

6. What are the sources for domperidone?

Domperidone is not approved for sale in the U.S. and is therefore considered an investigational drug. Investigational drugs can come from many sources including foreign and domestic pharmaceutical manufacturers. Authorization must be obtained from FDA prior to the importation, interstate shipment, and

administration of domperidone. To facilitate the process of importing domperidone which may otherwise be detained upon importation, FDA has identified suppliers and dispensing pharmacies (see Attachment A).

7. How can I get domperidone for my patient?

To obtain domperidone tablets, IND sponsors may contact any of the manufacturer suppliers listed in Attachment A for direct bulk drug product shipment.
For bulk drug product shipment to the sponsor, the sponsor name and IND number must be indicated on the entry documents provided to Customs at the time the product is offered for entry. The chosen supplier should label the shipment with the appropriate identification. If a shipment of domperidone is detained at the U.S. border by Customs or the FDA Import Office, questions should be referred to Heather Buck, Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products at (301) 796-1413.

Alternatively, for direct drug product shipment to the patient, the IND sponsor should provide the pharmacy supplier (see Attachment A) with a copy of the acknowledgement letter issued by the FDA. The patient may then contact the pharmacy to receive drug product directly or via mail order.

8. Can I charge for medications distributed under an IND?

U.S. regulations prohibit charging a patient for an investigational drug unless FDA gives authorization to do so. The FDA has determined that the investigational use of domperidone to treat patients with gastrointestinal disorders and who have failed standard therapy may qualify for drug cost recovery. **A request to charge must be made if the sponsor or pharmacy plans to charge the patient or health insurance provider for the cost of the drug.** In this case, cost recovery would extend only to the cost of the drug and associated shipping costs. Commercialization of an investigational drug is prohibited.

IND Sponsor-Investigators who wish to recover the cost of an investigational drug must submit a request to do so in the IND application. Sponsors may request to charge for domperidone under 21 CFR 312.8 by checking the box next to the charging request paragraph in the cover letter provided in this packet. The FDA will respond in writing with the authorization to charge. Note that under 21 CFR 312.8, the price charged may not be larger than necessary to recover costs of manufacture, research, development, and handling of the investigational drug; and that under 21 CFR 312.8, authorization to charge for an investigational drug may be withdrawn by FDA if we find that the conditions underlying the authorization are no longer satisfied.

9. How should I supply the required information for my IND application?

See attachments A-I**.**

Attachment A
Suppliers

Manufacturer Suppliers

Idis House
Churchfield Road
Weybridge
KT13 8DB
United Kingdom
Idis general office: 00441932824000, globalgs@idispharma.com
Contact: Marco Adey, Customer Service Advisor
+44 (0) 1932 824 123
madey@idispharma.com

Pharmascience Inc.
6111 Royalmount Avenue
Suite 100
Montreal, QC H4P 2T4
Canada

Contact: For pricing and availability
International Customer Service
Toll Free: 1-800-363-8805 (extension 3221 or 3089)
Fax: 514-340-0656
email: custintl@pharmascience.com

Contact for other inquiries: Sophie Tanguay, M.Sc., Senior Director, Global Regulatory Affairs
Toll Free: 1(800) 363-8805 (extension 5022)
Tel: (514) 340-5022
Fax: (514) 344-3454
email: stanguay@pharmascience.com

Pharmacy Suppliers

Dougherty's Pharmacy
5959 Royal Lane Suite 515
Dallas, Texas 75230
Contact: Simon Keen
(214) 373-5300
Toll free 800-734-1615
Fax (214) 739-0238
skeen@doughertys.com

Dougherty's Pharmacy Forest Park Location
11970 N. Central Expressway Suite 100
Dallas, TX 75243
Contact: Steven Pettit
(469) 248-1000
Fax (469) 248-1019
spettit@doughertys.com

Attachment B
New IND Cover Letter

[Date]

Donna Griebel, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
Central Document Room 5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Dear Dr. Griebel,

I am hereby submitting an Investigational New Drug application (IND) under section 505(i) of the Federal Food, Drug, and Cosmetic Act and in accord with 21 CFR 312 for domperidone tablets.

This application contains the following (*please check all that apply*):

- ☐ Form 1571
- ☐ Form 1572
- ☐ IRB information (box 5 of 1572)
- ☐ Clinical protocol
- ☐ Copy of Informed Consent planned for use
- ☐ Information about the drug

I plan to provide domperidone prescriptions to approximately _____ (#) patients under this IND.

The name and address of the supplier of the domperidone tablets to be administered under this IND is _____.

You must check the following box if you are requesting to charge for domperidone:

☐Permission is requested, under 21 CFR 312.8, to charge for the investigational drug used in the protocol submitted with this IND.

I claim a categorical exclusion from environmental assessment requirements (under 21 CFR 25.31[e]) for this IND. To my knowledge, no extraordinary circumstances exist.

Sincerely,

Attachment C
Form FDA 1571

A fillable Form FDA 1571 can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083533.pdf

The following applies to submitting a new IND for domperidone only. Follow the instructions on the form unless otherwise indicated below (numbers correspond to numbered boxes on form):

1. The Sponsor-Investigator is the person who takes responsibility for and initiates a clinical investigation. The Sponsor-Investigator may be a pharmaceutical company, a private or academic organization, or an individual. **A Sponsor-Investigator is an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is being administered or dispensed.** For administrative reasons, only one individual should be designated as Sponsor-Investigator. If a pharmaceutical company will be supplying the drug, but will not itself be submitting the IND, the company is not the Sponsor-Investigator.

7. Indication is **to treat patients with gastrointestinal disorders who have failed standard therapy**

8. Phase(s) is **N/A**

9-10. Leave blank

11. Check **Initial Investigational New Drug Application (IND)**

12. Check **Charge Request, 21 CFR 312.8** if the patient will be charged at all for the drug. Check **Intermediate Size Patient Population, 21 CFR 312.315** (unless only one patient will be treated, in that case you would check Individual Patient Non-Emergency 21 CFR 312.310).

13. Contents of the Application:

Items 2, 3, 4:
May be briefly addressed in the cover letter or in a summary

Item 5:
The Investigator's Brochure is a narrative description of the known safety and efficacy information relating to the investigational drug. If the drug to be used is a product approved for use by another country, the approved professional labeling (product insert) translated into English will suffice for the Investigator's Brochure.

Item 6a:
See Attachment F (Protocol)

Items 6b, 6c, 6d:
Included in Attachment D (form FDA 1572)

Items 7, 8, 9:
The investigational drug should only be obtained from one of the authorized manufacturer

suppliers (see attachment A). Therefore, items 7, 8, and 9 may be incorporated into the IND by reference to information the manufacturer supplier has on file with FDA. If the investigational drug is prepared or altered in any way after shipment by the manufacturer supplier, complete manufacturing (or compounding) and controls information, including information on sterility and pyrogenicity testing for parenteral drugs, must be submitted for that process (item 7). **Note that at the time of this printing, FDA does not authorize compounding or alteration of domperidone.**

15-16. For Sponsor-Investigator INDs, the investigator has this responsibility. Note that there are certain important commitments that the IND Sponsor-Investigator makes by signing the form FDA 1571, which are listed below box 15.

17-25. For a Sponsor-Investigator IND, the Sponsor-Investigator should be named and must sign the form. An original signature must be submitted.

Attachment D
Form FDA 1572

Form FDA 1572 with its attachments may satisfy Form FDA 1571, box 12, items 6 b-d. Information can be supplied in the form of attachments (such as a curriculum vitae) rather than entering that information directly onto the form, but this should be so noted under the relevant section numbers.

HOW TO FILL OUT THE FORM FDA 1572:

A fillable Form FDA 1572 can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

Follow instructions on form unless otherwise indicated below (numbers correspond to numbered boxes on form):

3-4. Name and address of facility where the clinical investigation(s) will be conducted and any clinical laboratory to be used

5. Insert the name and address of your Investigational Review Board (IRB) in this box. (See Attachment E)

6. List any residents, fellows, research nurses, or others assisting the physician

7. N/A

8. N/A

Attachment E
Investigational Review Board

What is an IRB?

Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research.

What are my responsibilities concerning IRBs under an IND?

Under the IND regulations (21 CFR 312), you must assure that an IRB that complies with FDA regulations (21 CFR 56) will be responsible for the initial and continuing review and approval of the proposed clinical protocol. You must also assure that you will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects and that you will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

What IRB information must I submit in the IND?

You must provide the name and address of the IRB that will be responsible for the review of your proposed clinical protocol on form FDA 1572 "Statement of Investigator."

How do I obtain IRB review?

You should submit your proposed clinical protocol to your institution's IRB for review and approval prior to conducting the clinical investigation. If you are not affiliated with an institution with an IRB (e.g. you are a physician in private practice), you may be able to obtain IRB review by submitting the research proposal to a community hospital, a university/medical school, an independent IRB, a local or state government health agency or other organizations. If IRB review cannot be accomplished by one of these means, you may contact the FDA for assistance (Human Subject Protection Branch: Catherine Parker at 301-796-5553).

Attachment F
Domperidone Protocol

Domperidone is a dopamine antagonist with gastroprokinetic properties; domperidone does not readily cross the blood-brain barrier.

Purpose:

To provide oral domperidone to patients ≥12 years of age where, according to the investigator's judgment, a prokinetic effect is needed for the relief of refractory gastroesophageal reflux disease with upper gastrointestinal (GI) symptoms, gastroparesis, and chronic constipation in patients whom the potential benefit may outweigh the risk of cardiovascular adverse reactions including QT prolongation, Torsades de Pointes, and death.

Objective:

To allow the use of domperidone by patients with gastrointestinal disorders who have failed standard therapy.

Inclusion Criteria:

1. Male or female
2. Age 12 and older
3. Symptoms or manifestations secondary to GERD (e.g., persistent esophagitis, heartburn, upper airway signs or symptoms or respiratory symptoms), gastrointestinal motility disorders such as nausea, vomiting, severe dyspepsia or severe chronic constipation that are refractory to standard therapy.
4. Patients must have a comprehensive evaluation to eliminate other causes of their symptoms.
5. Patient has signed informed consent for the administration of domperidone that informs the patient of potential adverse events including:
    - cardiac arrhythmias including QT prolongation and death
    - increased prolactin levels
    - extrapyramidal side effects
    - breast changes
    - There is a potential for increased risk of adverse events with the drugs listed in the domperidone protocol addendum (see Attachment F).

Exclusion Criteria:

History of, or current, arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes. Patients with minor forms of ectopy (PACs) are not necessarily excluded.

1. Clinically significant bradycardia, sinus node dysfunction, or heart block. Prolonged QTc (QTc > 450 milliseconds for males, QTc>470 milliseconds for females).
2. Hepatic dysfunction
3. Renal insufficiency
4. Clinically significant electrolyte disorders.
5. Gastrointestinal hemorrhage or obstruction
6. Presence of a prolactinoma (prolactin-releasing pituitary tumor).
7. Pregnant or breast feeding female
8. Known allergy to domperidone

Treatment Plan:

10-30 mg of oral domperidone administered QID. Patients should be started at the lowest dose and maintained at the lowest effective dose given the increased risk of serious cardiovascular reactions with increasing exposures of domperidone. Patients should be evaluated before doses are increased (see the Assessment and Monitoring Requirements for Domperidone INDs table below).

Withdrawal Criteria:

1. Patients may withdraw from the trial at any time.
2. Patients must be withdrawn for the following:
   - The patient withdraws consent.
   - While on treatment, EKGs demonstrate QTc> 450 milliseconds for males, QTc>470 milliseconds for females, or there is a change in QTc greater than or equal to 60 milliseconds from baseline.
   - Development of serious electrolyte abnormalities.
   - The patient is not receiving therapeutic benefit from domperidone.

(Please note that the reason for withdrawal must be reported)

Assessment and Monitoring Requirements for Domperidone INDs:

	Screening Visit	Every 2-Month Visit[1] (the first year)	Every 6-Month Visit[1] Thereafter
Informed Consent	X		
Inclusion/Exclusion Criteria	X		
Medical History	X	X	X
Physical Exam	X	X	X
12-Lead EKG	**See footnote #2: EKG Monitoring**		
Assessment of labs (CBC, liver panel, renal panel)	X[3]	X	X
Vital signs	X	X	X
(Re)Assessment of domperidone use (Benefit/Risk)		X	X
Review concomitant medication	X	X	X
Adverse events		X	X

1. **Required Additional Visits:**
   - ***If an increase in domperidone dose is being considered***, schedule an ***additional patient visit*** to perform each of the evaluations shown ***prior to increasing the domperidone dose***. In all patients whose domperidone dose was increased, perform each of the evaluations shown at an ***every 2-month visit for the first year after the domperidone dose was increased***, and then at an ***every 6-month visit thereafter***.
   - ***If considering starting any concomitant medication that may interact with domperidone***, schedule an ***additional patient visit*** to perform each of the evaluations shown ***prior to starting the concomitant medication*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone"). In all patients who have started any concomitant medication that may interact with domperidone, perform each of the evaluations shown at an ***every 2-month visit for the first year after the concomitant medication was started***, and then at an ***every 6-month visit thereafter***.
2. **EKG Monitoring:**

- Screening Visit:
  - A ***new 12-Lead EKG*** will be obtained at the Screening Visit.
- Assessment Immediately After Initiation of Domperidone:
  - ***In all patients***, a 12-Lead EKG will be obtained ***3 to 7 days after domperidone is started.***
  - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
- Routine EKG Monitoring on a Stable Dose of Domperidone:
  - ***In all patients***, obtain an EKG at an ***every 2-month visit for the first year***, and then at an ***every 6-month visit thereafter***.
  - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
- Additional EKG Requirements if a Domperidone Dose Increase is Being Considered:
  - ***In all patients***, a 12-Lead EKG will be obtained ***at the additional visit prior to increasing the domperidone dose***, and ***3 to 7 days after the domperidone dose is increased***.
  - Timing of the EKG will be ***1 hour after the first domperidone dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
  - ***In all patients whose domperidone dose was increased***, obtain an EKG at an ***every 2-month visit for the first year after the domperidone dose was increased***, and then at an ***every 6- month visit thereafter***.
- Additional EKG Requirements if Starting Any Concomitant Medication that May Interact With Domperidone:
  - ***In all patients,*** a 12-Lead EKG will be obtained ***prior to starting the concomitant medication*** and ***3 to 7 days after the concomitant medication is started*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone").
  - Timing of the EKG will be ***1 hour after the first domperidone or domperidone/concomitant medication dose of the day*** in which the EKG is done.
  - ***Patients with clinically significant changes in EKG's from baseline*** will be followed up with a ***repeat EKG***.
  - ***In all patients who have started concomitant medications*** (see list below in the section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone"), obtain an EKG at an ***every 2-month visit for the first year after the concomitant medication was started***, and then at an ***every 6-month visit thereafter***.

3. **Assessment of Labs**:
   - Screening Visit:
     - For the initial screening, ***lab values from the prior 3 months*** may be assessed.

Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone.
The following drugs are moderate and strong inhibitors of CYP3A4, and may increase the drug levels of domperidone. There is an increasing risk of clinically significant QT prolongation, Torsade de Pointes, and death with increasing levels of systemic domperidone:

1. Antidepressants: doxepin (Adapin®, Sinequan®, Zonalon®), clomipramire (Anafril®), amoxapine (Asendin®), trazodone (Desyrel®), venlafaxine (Effexor®), nefazodone (Serzone®), fluvoxamine (Luvox®), paroxetine (Paxil®), fluoxetine (Prozac®, Saerfem®), sertraline (Zoloft®), amitriptyline (Elavil®, Endep®, Etrafon®, Limbitrol®, Triavil®), maprotiline (Ludiomil®), desipramine (Norpramin®), nortriptyline (Pamelor®), trimipramine (Surmontil®), imipramine (Tofranil®), protriptyline (Vivactil®),
2. Anti-psychotics: haloperidol (Haldol®), chlorpromazine (Thorazine®, Ormazine®), chlorpromazine pimozide (Orap®), sertindole (Serlect®), quetiapine (Seroquel®), mesoridazine (Serentil®), perphenazine (Triavil®), lfluphenazine (Apo-Fluphenazine®, Modecate Concentrate®, Moditen®, Permitil®, PMS-Fluphenazine®, Prolixin®, Rho-Fluphenazine®), promazine (Sparine®), trifluoperazine (Stelazine®)
3. Anti-Emetics: prochlorperazine (Compazine®), thioridazine (Mellaril®), promethazine (Phenergan®), mesoridazine (Serentil®), thiethylperazine, (Torecan®), perphazine (Trilafon®), dolasetron (Anzemet®), dronabinol (Marinol®), droperidol (Inapsine®)
4. Anti-infective agents: erythromycin (such as E.E.S.®, E-Mycin®, Ilotycin® , Pediazole®, Aknemycin®), clarithromycin (Biaxin®), troleandomycin (TAO®), norfloxacin (Chibroxin®, Noroxin®), quinine sulfate, quinupristin and dalfopristin (Synercid®), pentamidine (Nebupent®, Pentacarinat®, Pentam®), sparfloxacin (Zagam®), grepafloxacin (Raxar®), azithromycin (Zithromax®), ofloxacin (Floxin®). Levofloxacin (Levaquin®)
5. Anti-Fungal Agents: fluconazole (Diflucan®), itraconazole (Sporanox®), ketoconazole (Nizoral®), miconazole (Micatin®, Monistat®), terconazole (Terazol®), ticonazole (Vagistat®), butaconazole (Femstat 3®)
6. Antivirals: foscarnet (Foscavir®)
7. Protease Inhibitors: indinavir (Crixivan®), amprenavir (Agenerase®), ritonavir (Norvir®), nelfinavir (Viracept®), saquinavir (Invirase®, Fortovase®),
8. Anti-Hypertensives: nicardipine (Cardene®), isradipine (Dynacrirc®), moexipril/ HCTZ (Uniretic®)
9. Calcium Channel Blockers: verapamil (Calan®), diltiazam (Cardizem®), diltiazem/enalapril (Teczem®), verapamil/trandolapril (Tarka®), tocainide (Tonocard®), bepridil (Vascor®)
10. Anti-Arrhythmics: disopyramide (Norpace®, Norpace CR®), quinidine (such as Quinidex®, Cardioquin®, Quinaglute®, Duraquin®), procainamide (Procanbid® , Procan®, Pronestyl®,), flecainide (Tambocor®), sotalol (Betapace®), bretylium (Bretylol®), amiodarone (Cordarone®), ibutilide (Corvert®), moricizine (Ethmozine®)
11. Diueretics: bumetanide (Bumex®), furosemide (Lasix®), torsemide (Demadex®), etharcrynic Acid (Edecrin®), chlorothiazide (Diuril®), Indapamide (Lozol®)
12. Antilipemics: Bepridil (Vascor®), mibefradil (Posicor®),
13. Hematological Agents: cilostazol (Pletal®)
14. Respiratory Agents: zafirlukast (Accolate®), salmetrol (Serevent®)
15. Gastrointestinal Agents: cimetidine (Tagamet®), cisapride (Propulsid®)
16. Antidiarrheal: octreotide (Sandostain®)
17. Antihistamines: azelastine (Astelin®), clemastine (Tavist®)
18. Migraine treatment: naratriptan (Amerge®), sumatriptan (Imitrex®), zolmitriptan (Zomig®)
19. Antimalarial: halofantrine
20. Muscle relaxants: tizanidine (Zanaflex®)
21. Miscellaneous: tamoxifen (Nolvadex®), warfarin (Coumadin®), phenytoin (Dilantin®), ziprasidone (Geodon®), risperidone (Risperdal®), formoterol fumarate (Foradil Aerolizer®), sildenafil (Viagra®)

Attachment G
Chemistry Information

The IND application need not contain any chemistry information because domperidone is approved for use and sale in another country, and the manufacturer supplier which is selected from the list in attachment A is in contact with the FDA.

Attachment H
Adverse Event Reporting

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act, and the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. Your responsibilities include the following.

- Communicating any unexpected fatal or immediately life-threatening reactions associated with use of this product, either by telephone (301-796-1413) or fax (301-796-9904) no later than 7 calendar days after initial receipt of the information.

- Submitting all serious, unexpected adverse experiences as well as results from animal studies that suggest significant clinical risk within 15 calendar days after initial receipt of this information [21 CFR 312.32]. You may submit your safety report using FDA Form 3500 or in narrative format with the title "IND Safety Report".

Definitions

"Associated with the use of the drug"- There is a reasonable possibility that the experience may have been caused by the drug.

"Disability" - A substantial disruption of a person's ability to conduct normal life functions.

"Life-threatening adverse drug experience"- Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.

"Serious adverse drug experience"- Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

"Unexpected adverse drug experience"- Any adverse drug experience, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Attachment I
Annual Report

As sponsor of this IND, you are responsible for submitting written progress reports, which are required at intervals not exceeding one year and are due within 60 days of the application anniversary date (i.e., the date you were allowed to proceed with treatment under your IND number). Please include:

- A brief summary of the status of each patient enrolled in the protocol as it relates to their use of domperidone. If there is more than one protocol, identify the protocol.
- The total number of subjects you plan to treat under the protocol; the number entered into treatment to date, and the number who dropped out of the study for any reason.
- A description of the general investigational plan for the coming year.

A draft letter is provided for your convenience.

Date IND #

Annual Report

Donna Griebel, M.D.,
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products, HFD-180
Central Document Room
5901B Ammendale Road
Beltsville, Maryland 20705-1266

Dear Dr. Griebel,

In compliance with 21 CFR 312.33, I am submitting an annual report to IND (please provide IND number) for domperidone submitted on (provide date the IND was submitted to FDA).

This annual report covers the time period from (for the first annual report, state the date you were permitted by FDA to administer domperidone) to (the ending date of your summary of treatment).

Title of protocol:
Status of each patient studied:
Number of patients planned for enrollment:
Number of patients enrolled to date:
Number of patients who dropped out:
General investigational plan for coming year:

If you have any questions, you may reach me at (provide phone number).

Sincerely,

Attachment J
Informed Consent

In the content of your Informed Consent Document, you must at a minimum address the following risks in addition to ensuring that all requirements of 21 CFR 50 are met. In doing so, you must capture the key safety issues associated with the following:

1. Cardiovascular Risks

2. Drug Interactions that Increase the Risk of Serious Adverse Reactions Associated with Domperidone including Torsade de Pointes, cardiac arrest, and death.

Although the original reports of cardiac arrhythmias, cardiac arrest, and sudden death were with the intravenous form of domperidone, there have also been similar reports with the oral form of domperidone. Also, concomitant use of moderate or strong CYP3A4 inhibitors can lead to increased concentrations of domperidone, and thus increase the risk of cardiac arrhythmias, cardiac arrest, and sudden death. See the list of drugs in the Protocol (Attachment F) section "Drug Interactions that Could Increase the Cardiovascular Risks of Domperidone".